# EXHIBIT 43

American Journal of
EPIDEMIOLOGY

Volume 147
Number 5
March 1, 1998



Sponsored by the Society for Epidemiologic Research

## REVIEWS AND COMMENTARIES

# Biologic Plausibility in Causal Inference: Current Method and Practice

Douglas L. Weed[1] and Stephen D. Hursting[2]

The primary prevention of human cancer relies on the idea that reducing a population's exposure to a causal risk factor will result in decreased cancer incidence (1). Among the many examples (2–4), perhaps the most familiar is cigarette smoking and lung cancer (5), declared a causal association in 1964 and for years the focus of public health interventions (6). Not all associations, of course, are causal, and not all exposure-cancer pairs are statistically associated. Hundreds, perhaps thousands of exposures have been studied, including infectious agents, environmental and occupational exposures, lifestyle factors (including diet), medications, and medical technologies. Some are now considered causal risk factors, others remain controversial (7). Still other exposures are no longer studied due to empirical refutation, evidence judged to be insufficient, or changes in research funding priorities.

An important step along the path from research on potential cancer-causing exposures to successful application of preventive interventions is an assessment of available evidence, which typically takes place in review papers and editorials, and is often referred to as causal inference. Causal conclusions, or causal judgments, are one result of the qualitative criteria-based causal inference methods used in these assessments (8, 9). Two closely-related sets of criteria remain the foundation for the current practice of causal inference: those proposed by the Surgeon General's committee in 1964 (10) and those described by Austin Bradford Hill in 1965 (11).

Advances in the biologic sciences and their integration with public health science in molecular epidemiology (12–19) make one causal criterion, biologic plausibility (sometimes called biologic coherence), an increasingly important consideration in causal inference. Despite the growing influence of this criterion, there has been little systematic study of the concept of biologic plausibility and almost nothing published about how it is used in the practice of causal inference.

In this commentary, we review the role of biologic plausibility in causal inference as described in the methodological literature, and then review how biologic plausibility is used in practice, i.e., in review papers assessing evidence on specific associations (smoking and cervical cancer, and vasectomy and prostate cancer). These represent a small fraction of associations relevant to cancer prevention, yet in each case, considerable interest has been generated regarding the biologic plausibility of the underlying causal hypothesis.

Our purpose is primarily to describe how the concept of plausibility is currently used—and how methodologists recommend that it be used. This will serve as a first step toward more detailed inquiries into central unanswered questions (20, 21), such as: How does a *plausible* mechanism differ from a *known* mechanism? How much and what kinds of biologic evidence are important in judging the plausibility of an association? How will advances in measurement technology and in our understanding of the cellular pro-

Received for publication October 10, 1997, and accepted for publication October 20, 1997.

Abbreviations: CI, confidence interval; IARC, International Agency for Research on Cancer.

[1]Chief, Preventive Oncology Branch, National Cancer Institute, Bethesda, MD.

[2]Departments of Epidemiology and Carcinogenesis, University of Texas-M. D. Anderson Cancer Center, Houston, TX.

Reprint requests to Dr. Douglas L. Weed, Chief, Preventive Oncology Branch, National Cancer Institute, EPS-T41, 6130 Executive Blvd., MSC 7105, Bethesda, MD 20892-7105.

cesses involved in initiation and tumor promotion change the way the criterion of biologic plausibility is interpreted and used? Because biologic plausibility is only one of several considerations important in making causal judgments, we are cautious not to make our own causal conclusions regarding the associations studied. We will, however, make some recommendations regarding the future role of biologic plausibility in the theory and practice of causal inference.

## Background: biologic plausibility in theory and methodology

An account of the role of biology in causal inference could begin about a century and a half ago with the works of Jakob Henle and his student, Robert Koch (22). The "Henle-Koch" postulates were an early description of empirically-based conditions for causes of infectious diseases and later became the starting point for discussions of causation in chronic diseases. In epidemiology, these discussions began in earnest in the 1950s, and from them two papers emerged in the mid-1960s which have had a sustained impact on the practice of causal inference in cancer epidemiology (9). In 1964, a US Surgeon General's committee used a set of five criteria to judge that smoking cigarettes caused lung cancer (10). One year later, Bradford Hill expanded this list to nine criteria—he called them "aspects of associations"—important to disease causation (11).

Both early accounts included a role for biology in causal inference. Coherence was the criterion of the Surgeon General's committee that incorporated the related notions of biologic mechanism and biologic plausibility. The approach is succinctly described in the committee's own wording:

> "Coherence is clearly established when the actual mechanism of disease is defined. Coherence exists, nevertheless, although of a lesser magnitude, when there is enough evidence to support a plausible mechanism, but not a detailed understanding of each step in the chain of events by which a given etiologic agent produces disease" (10, p. 20).

Hill distinguished between coherence and plausibility, although his views on the latter have been more influential in cancer epidemiology (23). Hill wrote:

> "It will be helpful if the cause. . .is biologically plausible. . .but we cannot demand it. What is biologically plausible depends upon the biological knowledge of the day" (11, p. 298).

Hill's words are echoed in a recent *Lancet* commentary by Glynn:

> "The existence of a suggested mechanism by which a proposed cause of a disease exerts its effect is reassuring. However, this will depend on the biological knowledge of the disease at the time. . ." (24, p. 531).

Hill's and Glynn's papers (11, 24), and many others published between 1965 and 1994 (25–32), reveal a commonly-held viewpoint, that in a given case (i.e., for a single factor-cancer association) *a biologically plausible association is one for which a reasonable mechanism can be hypothesized, but for which no biologic evidence may exist.* As such, biologic plausibility becomes a dispensable consideration. In support of this view, Schlesselman argues that biologic plausibility "may occasionally impede acceptance of new facts" and is a "conservative" criterion, used "either to dismiss some unexpected finding or to support an association from a study based on suspect methods" (29, p. 201). The dispensability of biologic plausibility also figures in decisions to publish the results of epidemiologic studies in some journals. An editor of the *New England Journal of Medicine* recently wrote that publication may be warranted for large effects that "do not make biologic sense" (33, p. 824). Note, however, that the endpoint is publication (not causation), and that a condition has been placed on at least one other causal criterion—here, magnitude of the association—in order to justify dispensing with biologic plausibility.

The rapid progress made in the fields of molecular biology and molecular epidemiology since the late 1980s has underscored a second way to represent biologic plausibility in causal inference (19, 34–38). *Many authors have argued that simply suggesting a mechanism for a factor-cancer association is insufficient. Evidence supporting the proposed mechanism is also necessary.* The International Agency for Research on Cancer (IARC), in a 1990 monograph, categorizes types of biologically relevant evidence (35). Emphasized are biologic indicators of exposure, such as DNA adducts or protein adducts and animal model evidence. In a recent paper, McMichael (19) examines the current capacity of molecular epidemiologic techniques to identify the biologically effective dose at tissue targets (e.g., DNA adducts), early biologic effects (e.g., mutations), and variations in individual susceptibility. He argues that evidence of prospective links between molecular events, especially DNA adducts and cancer occurrence, are important in causal assessments yet are rarely available. With regard to animal evidence (e.g., long-term bioassays in rodents), the IARC monograph discusses the strengths and limitations of this type of evidence, particularly the interspecies differences in susceptibility to chemically induced cancer and the extent to which genetic heterogeneity and other factors can be controlled.

A third, more rigorous, notion of biologic plausibility has also been proposed: *an association is considered biologically plausible if there is sufficient evidence to show how the factor influences a known disease mechanism* (30, 37). This is the most stringent of the three approaches to biologic plausibility relative to the "evidence-free" or "evidence-supportive" notions discussed above because it requires that the mechanism be defined to the extent that it is possible to examine the influence of the putative factor on the inner workings of that mechanism.

These three approaches help to organize the methodological work to date and reveal vastly different opinions on what counts as a biologically plausible association. It remains unclear how much and what kinds of evidence will turn a "suggested" (24) or "hypothesized" (36) mechanism into a "coherent" mechanism (10), i.e., one that not only "makes sense" (33) but one "defined. . .by our detailed understanding of each step in the chain of events" (10, p. 20). Similarly, what does it take to claim that we "know" a mechanism (30, 37)? We continue our search for answers to these central questions on the role of biologic evidence in human cancer causation not by proposing more theory (39, 40), but, rather, by examining two well-known exposure-cancer associations. For each we describe the evolution of evidence and the ways in which investigators, specifically those publishing review papers, have approached the concepts of biologic evidence, plausibility, and mechanism in causal inference.

## Materials and methods

The MEDLINE© database was searched from January 1977 through December 1996, using keywords, "causation," "causal inference," "biologic plausibility," "biologic mechanism," "smoking and cervical cancer," "and vasectomy and prostate cancer." Reviews, editorials, and methodological articles were also identified from reference lists of primary research studies and from chapters of general epidemiology, cancer epidemiology, and cancer prevention and control textbooks. In addition, tables of contents from major medical, public health, cancer, and epidemiology journals available at the National Institutes of Health were examined.

## Smoking and cervical cancer

Thirty-six case-control and six cohort studies on smoking and cervical cancer were published from 1966 through 1995 (41–83). Ten reviews (84–93), 12 mini-reviews (94–105), two meta-analyses (106, 107), and several related letters and commentaries have also appeared (108–110). We examined the 10 reviews and two meta-analyses published between 1977 and 1991, divided into three groups: 1977–1984, 1985–1986, and 1989–1991. Next we examined the "mini-reviews " published from 1991 through 1995; these are brief reviews of the association included within reviews of cervical cancer epidemiology, risk factors for gynecologic tumors, or reviews of the impact of smoking on cancer.

*Reviews of smoking and cervical cancer (1977–1984).* Winkelstein (84) suggested a possible association between smoking and cervical cancer in 1977 (84). Two biologic hypotheses were proposed: First, cervix cancer is primarily a squamous cell disease and smoking causes squamous cell carcinomas in many sites, including lung. Second, smoking constituents (especially carcinogens) may be transported to distant sites (including the cervical epithelium) via the circulation. No evidence was cited for either hypothesis. In 1981, however, Winkelstein (108) noted in a letter written in response to a charge that the association was implausible, findings of nicotine in the breast fluid of nonlactating smokers (111). In 1982, the Surgeon General's office reviewed the smoking and cervical cancer literature, concluding that it was unclear if an association existed (85). The report ignored the issue of biologic plausibility. One year later, Austin's review (86) cited epidemiologic evidence along with two studies regarding biologic plausibility: the study showing nicotine in breast fluid (111) mentioned above, and a study showing that inhaled mutagens are concentrated in the urine of smokers (112). Austin argued that "these studies adequately illustrate that epithelial cells must be perfused with smoke carcinogens via the circulation" (86, p. 516) and he declared that cervical cancer was caused by smoking and that preventive measures were needed. Finally, in 1984, Winkelstein et al. published a review whose stated purpose was to "examine the reluctance to accept an etiologic interpretation of the. . .association" (87, p. 2). They added a study showing mutagenicity of smokers' nipple aspirates (113) and concluded that there was strong evidence to consider smoking a risk factor for cervical cancer.

It is reasonable to conclude that in these early reviews of the smoking and cervical cancer association, biologic plausibility was used (86, 87) as a criterion for which evidence directly testing the biologic hypothesis was unnecessary to make a causal claim, consistent with the "evidence-free" approach mentioned above. Winkelstein et al. (87) and Austin (86) claimed that smoking caused cervical cancer with no direct evidence that smoking constituents reach the

cervical epithelium much less were responsible for carcinogenic changes.

*Reviews of smoking and cervical cancer (1985–1986).* Three reviews appeared during the years 1985–1986 (88–90). The IARC concluded—without reference to biologic plausibility—that ". . .the causal nature of the association. . .remains uncertain" (88, p. 298). The review also mentioned an alternative hypothesis, that "there is a specific causal agent—an infective agent transmitted sexually" (88, p. 298) so far unidentifed. The two reviews published in 1986 also mentioned this possibility, although both maintained that smoking was an independent causal factor (89, 90). With regard to biologic plausibility, both 1986 reviews cited evidence published a year earlier in the *New England Journal of Medicine* (114) showing concentrated nicotine and cotinine levels in the cervical mucus of smokers, thus providing the first direct biologic evidence of exposure to the cervix. In addition, Winkelstein (89) demonstrated that most cervical cancer is squamous, using Third National Cancer Survey data. Finally, the review by Singer and Tay (90 p. S89) argued that smoking may elicit a local immunosuppressive effect facilitating a persistent viral infection. They cited their own unpublished research and a paper describing reduced killer cell activity in male melanoma patients (115).

In terms of evidence-based biologic plausibility, the causal conclusions so strongly argued by Winkelstein (89) and by Singer and Tay (90) are based on a single study documenting that the target tissue is perfused with some chemicals arising from exposure to cigarette smoke. Interestingly, the IARC report mentioned this same biologic study in a separate section of its monograph, yet did not refer to it when concluding that causation was uncertain.

*Reviews and meta-analyses of smoking and cervical cancer (1989–1991).* By the time new reviews appeared in 1989 (91, 92), two major biologic hypotheses had emerged: that smoking causes cervical cancer by direct exposure of carcinogens to the cervical epithelium, and that smoking induces a local immunosuppressive effect facilitating a persistent viral infection. The Surgeon General's 1989 (91) review addressed only the direct exposure hypothesis, citing the 1985 *New England Journal of Medicine* study of nicotine and cotinine levels (114) and a study published 1 year later showing mutagenicity of cervical mucus in smokers (116). The report concluded that the association was consistent and plausible but did not claim causation. Later in 1989, Layde (92) also ignored the immunosuppression hypothesis, citing the now-familiar *New England Journal of Medicine* 1985 study (114) and a study confirming the finding that cervical mucus in smokers is mutagenic (117). Layde reviewed the IARC (88) and the Surgeon General's (91) decisions, claiming that confounding by an unknown yet likely viral factor was responsible for the cautious decisions found there. He concluded with a public health recommendation that women should stop smoking for many reasons (besides avoiding risk of cervical cancer).

Three papers appeared in 1990, a meta-analysis (106), a review (93), and a commentary on the review (109). The meta-analysis examined six case-control studies of histologically confirmed invasive cervical cancer. The summary odds ratio for current smokers was 1.81 (confidence interval (CI) 1.54–2.12) with no significantly elevated risk in former smokers. Without reference to biologic plausibility, the authors concluded that the "results provide additional rationale for health care professionals. . .to give antismoking messages to their patients" (109, p. 280).

Winkelstein's fourth review on this topic (93) featured a discussion of the 15 epidemiologic studies published since his 1986 review (89) and an extended discussion of biologic plausibility. Winkelstein reiterated three biologic hypotheses: that smoking-related cancers (including cervical cancer) are squamous, that carcinogenic chemicals in smoke reach the cervical epithelium, and that smoking may act as a cofactor with a viral agent. To buttress the first of these, Winkelstein added findings from a study done in 1962 (118) showing that smoking-related cancers occur as second primaries more frequently in women with primary cancer of the cervix than nonsmoking related cancers (87). Evidence of smoke constituents in cervical epithelium (117, 119) was included for the direct exposure hypothesis. Winkelstein's treatment of the immunosuppressive hypothesis included four studies from the late 1980s (120–123) including a study (123) showing reductions in Langerhans cells in smokers with normal cervical epithelium and in smokers positive for human papilloma virus infection. To these three hypotheses, Winkelstein added a fourth: that smokers' lower serum $\beta$-carotene levels, perhaps from a deficiency of dietary vitamin A, may increase susceptibility to carcinogens. He noted that the epidemiologic evidence regarding this hypothesis was "equivocal" and offered no biologic evidence. In his conclusion, Winkelstein argued that "cervical cancer should be added to the list of smoking-related diseases" (93, p. 955) and that disease control strategies should include considerations of the etiologic role of cigarette smoking. In response to Winkelstein's review, Brinton argued that causality was uncertain due to three issues: confounding (by the effects of human papillomavirus infection), effect modification (by di-

etary factors), and the lack of information regarding biologic mechanisms (109). Indeed, Brinton emphasized that "caution must be exercised with regard to biologic plausibility" (109, p. 959) although she acknowledged that the smoking effect could be due to direct exposure or to immunosuppression.

Finally, in 1991, Sood (107) published a meta-analysis of eight case-control studies; the overall odds of cervical cancer was 1.42 (CI 1.33–1.51). With two references to the direct exposure biologic hypothesis (114, 116), Sood concluded that "smoking cessation advice to reduce the risk of all cancer, including perhaps cervical cancer, seems justified" (107, p. 211).

It is reasonable to conclude that during 1989–1991 the authors of reviews and meta-analyses were highly selective in their choice of biologic hypotheses and the evidence cited to support them. Of the six papers examined, four (91, 92, 106, 107) completely ignored the so-called "immunosuppressive" hypothesis. Indeed, one reviewer made public health recommendations without considering any biologic hypothesis (106). Finally, in the 1990 review (93) and accompanying commentary (109), the authors made different causal judgments from the same set of biologic hypotheses and similar evidence, with Winkelstein advising action and Brinton caution.

*Biologic evidence and mini-reviews (1992–1995).* No full review was published on the smoking and cervical cancer association after 1990. Nevertheless, several studies examining biologic hypotheses (124–132) and several "mini-reviews" (98–103) appeared between 1990 and 1995. In this section, we describe how the "mini-reviews" handled the issue of biologic plausibility in the face of accumulating biologic evidence. Studies confirming elevated nicotine levels in smokers' and passive smokers' cervical mucus samples appeared in 1991 (124) and 1992 (126), respectively. Studies showing that smoking increases exfoliation of cervicovaginal epithelial cells, and a follow-up study showing that smoking was not related to mutagenicity of cervical mucus, were published in 1992 (125) and 1993 (128), respectively. Then, in 1993, two studies revealed elevated smoking-related DNA adducts in cervical epithelium (129, 130), evidence which an epidemiologic commentator (19) noted strengthened the biologic plausibility of the association.

Yet not one of the three mini-reviews published in 1995 cited the DNA adduct evidence. Daly et al. (103) cited two studies of cervical mutagenicity published in 1987 and 1988, respectively (regarding the direct exposure hypothesis), as well as one study regarding the immunosuppressive hypothesis (123). Bornstein et al. (104) cited three late 1980s studies of the direct exposure hypothesis (114, 116, 117). Shopland (105) cited no biologic evidence. Earlier mini-reviews (100–102), published too early to have the 1995 DNA adduct evidence available, cited, among them, exactly one study regarding biologic plausibility: the 1988 Hellberg et al. study showing mutagenicity of cervical mucus (117).

*Summary findings.* Overall, many reviewers ignored some or all of the biologic hypotheses (and the available biologic evidence). Reviewers apparently used different definitions of "biologic plausibility" in their assessments, although no reviewer stated up front how much evidence and what types "count" in making causal judgments. In terms of the three approaches to biologic plausibility discussed in the earlier methodology section of this commentary, many reviewers inferred causation without biologic evidence to support the hypothesis. At least one reviewer (109) appeared to have a more stringent definition for biologic plausibility. No reviewer mentioned, much less described, an underlying model of carcinogenesis and the way in which the biologic evidence cited related to various steps or processes within that model.

The extent to which these findings are generally representative of the use of the criterion of biologic plausibility in the practice of causal inference in epidemiology is an interesting question. To help answer it, we turn to another association, vasectomy and prostate cancer.

## Vasectomy and prostate cancer

Studies of morbidity and mortality rates in vasectomized men appeared in the late 1970s and early 1980s (133–136), and three case-control studies (137–139) and a cohort study (140) had also been published in the 1980s. Of these, one case-control study (138) anticipated the concern about a possible relation between vasectomy and prostate cancer. That concern was fostered in 1990 after two positive case-control studies (141, 142) and an accompanying commentary (143) appeared in the *American Journal of Epidemiology*. The studies revealed statistically significant though modest evidence of an association. Soon thereafter, opinion papers appeared from the American Urological Association (144) and from a meeting of the World Health Organization (145) convened to examine the safety of vasectomy. Since 1991, five additional case-control studies have appeared (146–150) and seven reports from six separate cohort studies have been published (151–157). In addition, over 20 publications—editorials, reviews, mini-reviews, and papers specifically focussed on the issue of biologic mechanisms—have appeared (143, 145, 148–177).

The ways in which biologic plausibility and the closely related notion of biologic mechanisms were used in these publications published between 1990 and 1995 exactly parallel the situation in the smoking and cervical cancer literature with one important exception. As before, reviewers selectively examined biologic hypotheses and the biologic evidence available. Some reviewers, for example, mentioned only the possibility that vasectomy might raise testosterone levels. Others examined as many as four different biologic mechanisms: endocrine effects, antisperm antibodies, secretory flow effects, and growth factor inhibitors (167). For any given explanation (i.e., mechanism) the extent of evidence cited varied considerably. Furthermore, no reviewer discussed how he or she approached the concept of biologic plausibility nor described rules of inference for this important causal criterion. In contrast to the smoking and cervical cancer example, however, no reviewer of the vasectomy and prostate cancer association made a causal claim. Indeed, lack of convincing biologic evidence for any of several mechanisms was a common argument against assigning causality (or even risk factor status) to the surgical procedure regardless of the epidemiologic study results.

## Discussion

These two examples, involving causal assessments of well publicized associations in peer-reviewed review papers, reveal a large variability in how much attention reviewers devote to existing biologic hypotheses and evidence. Nothing remotely resembling a coherent set of rules for judging biologic evidence appears. Certainly, no reviewer specified a rule for using biologic plausibility as a causal criterion beyond that which is implied from occasional references to Hill's early papers or other similarly nonspecific approaches. This lack of methodological specification mirrors the general practice of causal inference inasmuch as reviewers rarely (if ever) propose in advance what specific rules they use when judging causation (23). Part of the problem, of course, is that for biologic plausibility we suspect that no comprehensive set of rules have *ever* been proposed, in practice or in theory.

Careful consideration of several issues will be necessary to make progress in this important area. Improving the quality of literature reviews and meta-analyses (178, 179) is a first step. Comprehensively examining and summarizing the conclusions of existing reviews, including conclusions about biologic plausibility, is part of a high quality (i.e., systematic) review paper. All previously proposed potential biologic explanations (i.e., mechanisms) would be available to the reviewer. Of course, reviewers may wish to propose a new mechanism or may exclude one or another biologic hypothesis. In a systematic review, however, reasons for exclusions are made specific in the methods section, e.g., that a hypothesis is not considered because no evidence is available.

Another component of a high quality review is stating how (and with what criteria and evidentiary rules) causal assessments will be made, but we have already discussed the lack of specification of such rules in the methodological literature and in practice. Indeed, we recognize that making judgments about specific exposure-cancer associations may be partially dependent upon the specifics of the situation; an exposure-cancer association, for example, may have unique biologic characteristics requiring unique decisions. On the other hand, if cancer has core processes that are near universal (i.e., occurring with limited variation across many tumor types) then general rules may be possible and obviously useful. Such rules will likely emerge from our expanding understanding of the nature of cancer biology combined with general theories of scientific reasoning and methodology.

It is beyond the purview of this commentary to carefully explore the theoretical foundations of contemporary biologic science as a first step toward proposing new rules of inference for the criterion of biologic plausibility. Nevertheless, a discussion of biologic mechanism and its role in scientific explanation may pave the way for a more detailed inquiry into the ways in which evidence of key events in the development of cancer would make a causal conclusion highly defensible.

We begin with consideration of the term "biologic," which refers (rather arbitrarily) to events occurring within the individual organism; we reserve the terms "behavioral" and "social" to refer to events occurring to individuals or populations, respectively (180). A biologic mechanism, therefore, refers to a series of events within the individual that (from some combination of inherited and acquired factors and processes) produce a malignancy. Our current understanding of the organizational structure of scientific knowledge comprising human cancer biology, however, includes a vast number of explanatory levels that contribute to the mechanism. Put another way (and in the context of smoking and lung cancer), the act of smoking (a socially mediated behavioral phenomenon influenced by the biology of addiction) begins the "biologic mechanism," which can then be described in terms of many different levels of explanation including the physical exposure of epithelial surfaces to smoke, the physical movement of smoke constituents throughout the vascular system, metabolism in tissues and organs, absorption across cellular membranes and throughout

intracellular spaces, and exposure to chromosomes, genes, and nucleic acids. At even deeper levels, there is the formation of DNA-adducts and subsequent alteration in electron and magnetic fields around the atoms making up the DNA molecules. What happens next, after the exposure (i.e., a specific chemical component of smoke or its metabolite) attaches itself to nucleic acid, is typically described in terms of DNA damage, which if not repaired can result in alterations in critical genes, such as tumor suppressor genes and oncogenes. In addition, a host of promoting factors (and competing prevention factors such as micronutrients and phytochemicals) interact with intracellular regulators of cell growth or apoptosis, which determine cell number homeostasis. Dysregulation of these cellular growth and death processes provides the opportunity for the clonal growth of a malignancy from a cell in a tissue in an organ which, eventually, signals to its host that something is amiss through a persistent cough, a dull ache in the chest, or due to an equally complex cascade of behaviorally and socially mediated events, a slight shadow on a radiograph.

Given this systems-oriented structural organization of "ecologic" knowledge (181), what constitutes a biologically plausible mechanism? If by "plausible" we mean "known," as in "fully described at all levels of scientific explanation," then a "known" biologic mechanism is orders of magnitude more complex than what was (inadequately) described in a single paragraph. Thus, the idea that an association is biologically plausible when the mechanism is "known," and sufficient evidence exists to show how the presumed causal factor affects it (30, 37), is too stringent (i.e., overdemanding) to be practically useful. Put another way, with the current lack of understanding of the complexity of cancer biology, no association can be declared plausible using an inferential rule that "each step" in the process, from first exposure to first clinical sign, must be defined.

Any judgment regarding biologic plausibility in the practice of causal inference in epidemiology will be made from evidence collected not only on a subset of the total number of events relevant to the occurrence of cancer, but also on a subset of the levels of explanation involved. Although others in molecular epidemiology have proposed ways to simplify the situation by combining various levels (18), two key concerns remain: at which levels is evidence relatively more important than others, and, at any given level, what is the best (i.e., strongest) type of evidence? In-depth discussions of these issues will require a look at the evolution of methodological technique in molecular and cellular biology and its relation to epidemiologic methodologies.

## Conclusion

For that part of the theory and practice of causal inference referred to as "biologic plausibility," progress will likely be made along two broad fronts: by improving the quality of literature reviews such that all biologic hypotheses and accompanying evidence are considered when judgments are made, and by using our expanded understanding of the complex layering of interactive systems that make up the biology of cancer to propose new rules of evidence applicable to the wide range of biologic research results examined in causal assessments.

## ACKNOWLEDGMENTS

The authors thank Dr. Margaret Spitz for her comments and suggestions on an earlier draft of the manuscript.

## REFERENCES

1. Garfinkel L. Perspectives on cancer prevention. CA 1995; 45:5–7.
2. Berlin NI. The prevention of cancer—a sobering perspective. J Clin Epidemiol 1994;47:573–4.
3. Cole P, Sateren W. The evolving picture of cancer in America. J Natl Cancer Inst 1994;87:159–60.
4. Cole P, Amoateng-Adjepong Y. Cancer prevention: accomplishments and prospects. Am J Public Health 1994;84:8–10.
5. Shopland DR. Tobacco use and its contribution to early cancer mortality with a special emphasis on cigarette smoking. Environ Health Perspect 1995;103(Suppl 8):131–42.
6. Orleans CT. Preventing tobacco-caused cancer: a call to action. Environ Health Perspect 1995;103(Suppl 8):149–52.
7. Samet JM. Controlling the avoidable causes of cancer: needs and opportunities for etiologic research. Environ Health Perspect 1995;103(Suppl 8):307–11.
8. Susser M. Judgment and causal inference: criteria in epidemiologic studies. Am J Epidemiol 1977;105:1–15.
9. Weed DL. Causal and preventive inference. In: Greenwald PG, Kramer BS, Weed DL, eds. Cancer prevention and control. New York, NY: Marcel Dekker, 1995:285–302.
10. US Surgeon General's Advisory Committee on smoking and health. US Department of Health, Education, and Welfare, Public Health Service. Washington, DC: US GPO, 1964. (DHHS publication no. (PHS) 1103).
11. Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965;58:295–300.
12. Perera FP, Weinstein IB. Molecular epidemiology and carcinogen-DNA adduct formation: new approaches to studies of human cancer causation. J Chronic Dis 1982;35: 581–600.
13. Perera FP. Molecular cancer epidemiology: a new tool in cancer prevention. J Natl Cancer Inst 1987;78:887–98.
14. Schulte PA. Methodologic issues in the use of biologic markers in epidemiologic research. Am J Epidemiol 1987; 126:1006–16.
15. Hulka BS, Wilcosky TC, Griffith JD. Biological markers in epidemiology. New York, NY: Oxford University Press, 1990.
16. Hulka BS. Epidemiological studies using biological markers: issues for epidemiologists. Cancer Epidemiol Biomarkers Prev 1991;1:13–19.

17. Shields PG, Harris CC. Molecular epidemiology and the genetics of environmental cancer. JAMA 1991;266:681–7.
18. Schulte PA, Perera FP. Molecular epidemiology: principles and practices. San Diego, CA: Academic Press, 1993.
19. McMichael AJ. Invited commentary—"Molecular epidemiology": new pathway or new traveling companion? Am J Epidemiol 1994;140:1–11.
20. Weed DL. Between science and technology: the case of antihistamines and cancer. (Editorial). J Natl Cancer Inst 1994;86:740–1.
21. Weed DL. On the use of causal criteria. Int J Epidemiol 1997;26:1137–41.
22. Evans AS. Causation and disease. New York, NY: Plenum Medical, 1993.
23. Weed DL, Gorelic LS. The practice of causal inference in cancer epidemiology. Cancer Epidemiol Biomarkers Prev 1996;5:303–11.
24. Glynn JR. A question of attribution. Lancet 1993;342:530–2.
25. Sackett DL. The diagnosis of causation. In: Gent M, Shigematsu I, eds. Epidemiological issues in reported drug-induced illnesses—SMON and other examples. Hamilton, Ontario, Canada: McMaster University Library Press, 1978: 106–17.
26. Department of Clinical Epidemiology and Biostatistics, McMaster University Health Sciences Centre. How to read clinical journals. IV. To determine etiology or causation. Can Med Assoc J 1981;124:985–90.
27. Rothman KJ. Modern epidemiology. Boston, MA: Little Brown, 1986.
28. Susser M. The logic of Sir Karl Popper and the practice of epidemiology. Am J Epidemiol 1986;124:711–18.
29. Schlesselman JJ. "Proof" of cause and effect in epidemiological studies: criteria for judgment. Prev Med 1987;16: 195–210.
30. Elwood JM. Causal relationship in medicine: a practical system for critical appraisal. New York, NY: Oxford University Press, 1988.
31. Gordis L. Challenges to epidemiology in the next decade. Am J Epidemiol 1988;128:1–9.
32. Savitz DA. In defense of black box epidemiology. Epidemiology 1994;5:550–2.
33. Angell M. The interpretation of epidemiologic studies. N Engl J Med 1990;323:823–5.
34. Vandenbroucke JP. Is "the causes of cancer" a miasma theory for the end of the twentieth century? Int J Epidemiol 1988;17:708–9.
35. Defining cause. In: Tomatis L, ed. Cancer: causes, occurrence and control. Lyon, France: International Agency for Research on Cancer, 1990:97–125. (IARC scientific publication no. 100).
36. Susser M. What is a cause and how do we know one? A grammar for pragmatic epidemiology. Am J Epidemiol 1991; 133:635–48.
37. Renton A. Epidemiology and causation: a realist view. J Epidemiol Community Health 1994;48:79–85.
38. Skrabanek P. The emptiness of the black box. Epidemiology 1994;5:553–5.
39. Weed DL. Epistemology and ethics in epidemiology. In: Coughlin SS, Beauchamp TL, eds. Ethics and epidemiology. New York, NY: Oxford University Press, 1996:76–94.
40. Weed DL. Underdetermination and incommensurability in contemporary epidemiology. Kennedy Inst Ethics J 1997;7: 107–27.
41. Naguib SKM, Landin FE Jr, Davis HJ. Relation of various epidemiologic factors to cervical cancer as determined by a screening program. Obstet Gynecol 1966;28:4551–9.
42. Tokuhata GK. Tobacco and cancer of the genitalia among married women. Am J Public Health 1967;57:830–9.
43. Newman G. Early diagnosis of cancer of the cervix—the detection of high-risk patients. Geburtshilfe Frauenheilkd 1972;32:574–8.
44. Thomas DB. An epidemiologic study of carcinoma in situ and squamous dysplasia of the uterine cervix. Am J Epidemiol 1973;98:10–28.
45. Kessler II, Kulcar Z, Zimolo A, et al. Cervical cancer in Yugoslavia. II. Epidemiologic factors of possible etiologic significance. J Natl Cancer Inst 1974;53:51–60.
46. Williams RR, Horm JW. Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the Third National Cancer Survey. J Natl Cancer Inst 1977;58:525–47.
47. Buckley JD, Harris RWC, Doll R, et al. Case-control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. Lancet 1981;2:1010–15.
48. Wigle DT, Mao Y, Grace M. Re: "Smoking and cancer of the uterine cervix: hypothesis." (Letter). Am J Epidemiol 1980; 111:125–7.
49. Harris RWC, Brinton LA, Cowdell RH, et al. Characteristics of women with dysplasia or carcinoma in situ of the cervix uteri. Br J Cancer 1980;42:359–69.
50. Stellman SD, Austin H, Wynder EL. Cervix cancer and cigarette smoking: a case-control study. Am J of Epidemiol 1980;111:383–8.
51. Clarke EA, Morgan RW, Newman AM. Smoking as a risk factor in cancer of the cervix: additional evidence from a case-control study. Am J Epidemiol 1982;115:59–66.
52. Lyon JL, Gardner JW, West DW, et al. Smoking and carcinoma in situ of the uterine cervix. Am J Public Health 1983;73:558–62.
53. Trevathan E, Layde P, Webster LA, et al. Cigarette smoking and dysplasia and carcinoma in situ of the uterine cervix. JAMA 1983;250:499–502.
54. Berggren G, Sjostedt S. Preinvasive carcinoma of the cervix uteri and smoking. Acta Obstet Gynecol Scand 1983;62: 593–8.
55. Marshall JR, Graham S, Byers T, et al. Diet and smoking in the epidemiology of cancer of the cervix. J Natl Cancer Inst 1983;70:847–51.
56. Hellberg D, Valentin J, Nilsson S. Smoking as a risk factor in cervical neoplasia. (Letter). Lancet 1983;2:1497.
57. Martin PMD, Hill GB. Cervical cancer in relation to tobacco and alcohol consumption in Lesotho, Southern Africa. Cancer Detect Prev 1984;7:109–14.
58. Vonka V, Kanka J, Hirsch I, et al. Prospective study on the relationship between cervical neoplasia and herpes simplex type-2 virus. II. Herpes simplex type-2 antibody presence in sera taken at enrollment. Int J Cancer 1984;33:61–6.
59. Reeves WC, Brinton LA, Brenes MM, et al. Case-control study of cervical cancer in Herrera Province, Republic of Panama. Int J Cancer 1985;36:55–60.
60. Mayberry RM. Cigarette smoking, herpes simplex virus type 2 infection, and cervical abnormalities. Am J Public Health 1985;75:676–8.
61. Zunzunegui MV, King MC, Coria CF, et al. Male influences on cervical cancer risk. Am J Epidemiol 1986;123:302–7.
62. Peters RK, Thomas D, Hagan DG, et al. Risk factors for invasive cervical cancer among Latinas and non-Latinas in Los Angeles County. J Natl Cancer Inst 1986;77:1063–77.
63. La Vecchia C, Franceschi S, Decarli A, et al. Cigarette smoking and the risk of cervical neoplasia. Am J Epidemiol 1986;123:22–9.
64. Zaninetti P, Franceschi S, Baccolo M, et al. Characteristics of women under 20 with cervical intra-epithelial neoplasia. Int J Epidemiol 1986;15:477–81.
65. Baron JA, Byers T, Greenberg ER, et al. Cigarette smoking in women with cancers of the breast and reproductive organs. J Natl Cancer Inst 1986;77:677–80.
66. Brinton LA, Schairer C, Haenszel W, et al. Smoking and invasive cervical cancer. JAMA 1986;255:3265–9.
67. Brinton LA, Tashima KT, Lehman HF, et al. Epidemiology of cervical cancer by cell type. Cancer Res 1987;47: 1706–11.
68. Celentano DD, Klassen AC, Weisman CS, et al. The role of contraceptive use in cervical cancer: the Maryland Cervical

Cancer Case-Control Study. Am J Epidemiol 1987;126: 592–604.
69. Reeves WC, Caussy D, Brinton LA, et al. Case-control study of human papillomaviruses and cervical cancer in Latin America. Int J Cancer 1987;40:450–4.
70. Nischan P, Ebeling K, Schindler C. Smoking and invasive cervical cancer risk: results from a case-control study. Am J Epidemiol 1988;128:74–7.
71. Slattery ML, Robison LM, Schuman LK, et al. Cigarette smoking and exposure to passive smoking are risk factors for cervical cancer. JAMA 1989;261:1593–8.
72. Licciardone JC, Wilkins JR III, Brownson RC, et al. Cigarette smoking and alcohol consumption in the aetiology of uterine cervical cancer. Int J Epidemiol 1989;18:53–7.
73. Brisson J, Roy M, Fortier M, et al. Condyloma and intraepithelial neoplasia of the uterine cervix: a case-control study. Am J Epidemiol 1988;128:337–42.
74. Brock KE, MacLennan R, Brinton LA, et al. Smoking and infectious agents and risk of in situ cervical cancer in Sydney, Australia. Cancer Res 1989;49:4925–8.
75. Jones J, Brinton LA, Hamman RF, et al. Risk factors for in situ cervical cancer: results from a case control study. Cancer Res 1990;50:3657–62.
76. Herrero R, Brinton LA, Reeves WC, et al. Invasive cervical cancer and smoking in Latin America. J Natl Cancer Inst 1989;81:205–11.
77. Hirayama T. Operational aspects of cancer public education in Japan. In: Summary Proceedings of the International Conference on Public Education About Cancer. UICC Technical Report Series. Vol 18. Geneva, Switzerland: International Union Against Cancer, 1975:85–90.
78. Hirayama T. Changing patterns of cancer in Japan with special reference to the decrease in stomach cancer mortality. In: Hiatt HH, Watson JD, Winsten JA, eds. Origins of human cancer. Book A: Incidence of cancer in humans. Cold Spring Harbor Conference on Cell Proliferation. Vol 4. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1977:55–75.
79. Cederlof R, Friberg I, Hrubec Z, et al. The relationship of smoking and some social covariables to mortality and cancer morbidity: a ten year follow-up in a probability sample of 55,000 Swedish subjects ages 18 to 69. Stockholm, Sweden: Department of Environmental Hygiene, The Karlinska Institute, 1975.
80. Wright NH, Vessey MP, Kenward B, et al. Neoplasia and dysplasia of the cervix uteri and contraception: a possible protective effect of the diaphragm. Br J Cancer 1978;38: 273–9.
81. Garfinkel L. Cancer mortality in nonsmokers: prospective study by the American Cancer Society. J Natl Cancer Inst 1980;65:1169–73.
82. Greenberg ER, Vessey M, McPherson K, et al. Cigarette smoking and cancer of the uterine cervix. Br J Cancer 1985; 51:139–41.
83. Gram IT, Austin H, Stalsberg H. Cigarette smoking and the incidence of cervical intraepithelial neoplasia, grade III, and cancer of the cervix uteri. Am J Epidemiol 1992;135:341–6.
84. Winkelstein W Jr. Smoking and cancer of the uterine cervix: hypothesis. Am J Epidemiol 1977;106:257–9.
85. Shopland DR: The health consequences of smoking. Cancer: a report of the Surgeon General. US Department of Health and Human Services, Public Health Service, Office on Smoking and Health. Washington, DC: US GPO, 1982; 137–141. (DHHS publication no. (PHS) 82–50179).
86. Austin DF. Smoking and cervical cancer. JAMA 1983;250: 516–17.
87. Winkelstein W Jr, Shillitoe EJ, Brand R, et al. Further comments on cancer of the uterine cervix, smoking, and herpesvirus infection. Am J Epidemiol 1984;119:1–8.
88. Tobacco smoking. In: IARC monograph on the evaluation of the carcinogenic risk of chemicals to humans. Vol 38. Lyon, France: International Agency for Research on Cancer, 1985: 282–92.
89. Winkelstein W Jr. Cigarette smoking and cancer of the uterine cervix. In: Hoffman D, Harris CC, eds. Mechanisms in tobacco carcinogenesis. Banbury report 23. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1986:329–41.
90. Singer A, Tay SK. Smoking and cervical neoplasia: a serious public health problem. J Obstet Gynaecol 1986;6(Suppl 2): S89–90.
91. Reducing the health consequences of smoking: 25 years of progress. A report of the Surgeon General: 1989 Executive Summary. Rockville, MD: US Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office of Smoking and Health, 1989:57–8. (DHHS publication no. (CDC) 89–8411).
92. Layde PM. Smoking and cervical cancer: cause or coincidence? JAMA 1989;261:1631–3.
93. Winkelstein W Jr. Smoking and cervical cancer—current status: a review. Am J Epidemiol 1990;131:945–57.
94. Chamberlain G. Aetiology of gynaecological cancer. J R Soc Med 1981;74:246–61.
95. Brinton LA, Fraumeni JF. Epidemiology of uterine cervical cancer. J Chronic Dis 1986;39:1051–65.
96. Lovejoy NC. Precancerous lesions of the cervix: personal risk factors. Cancer Nurs 1987;10:2–14.
97. McMichael AJ, Hiller JE. Pills, partners and preventive prospects: in-situ cancer of the cervix. Med J Aust 1989;150: 114–16.
98. Einhorn N. Risk factors and etiology in gynecologic cancer. Curr Opin Oncol 1990;2:857–63.
99. Trope CG, Makar AP. Epidemiology, etiology, screening, prevention, and diagnosis in female genital cancer. Curr Opin Oncol 1991;3:908–19.
100. Yoder L, Rubin M. The epidemiology of cervical cancer and its precursors. Oncol Nurs Forum 1992;19:485–93.
101. Graham CA. Cervix cancer prevention and detection update. Semin Oncol Nurs 1993;9:155–62.
102. Shopland DR, Burns DM. Medical and public health implications of tobacco addiction. In: Orleans CT, Slade J, eds. Nicotine addiction: principles and management. New York, NY: Oxford University Press, 1993:105–28.
103. Daly MB, Bookman MA, Lerman CE. Female reproductive tract: cervix, endometrium, ovary. In: Greenwald P, Kramer BS, Weed DL, eds. Cancer prevention and control. New York, NY: Marcel Dekker, 1995:585–610.
104. Bornstein J, Rahat MA, Abramovici H. Etiology of cervical cancer: current concepts. Obstet Gynecol Surv 1995;50: 146–54.
105. Shopland DR. Tobacco use and its contribution to early cancer mortality with a special emphasis on cigarette smoking. Environ Health Perspect 1995;103(Suppl 8):131–42.
106. Licciardone JC, Brownson RC, Chang JC, et al. Uterine cervical cancer risk in cigarette smokers: a meta-analytic study. Am J Prev Med 1990;6:274–81.
107. Sood AK. Cigarette smoking and cervical cancer: meta-analysis and critical review of recent studies. Am J Prev Med 1991;7:208–13.
108. Winkelstein W Jr. Smoking and cancer of the cervix. (Letter). Br J Cancer 1981;43:736.
109. Brinton LA. Editorial commentary: smoking and cervical cancer—current status. Am J Epidemiol 1990;131:958–60.
110. Phillips AN, Davey Smith G. Cigarette smoking as a potential cause of cervical cancer: has confounding been controlled? Int J Epidemiol 1994;23:42–9.
111. Petrakis NL, Gruenke LD, Besten TC. Nicotine in breast fluid of nonlactating women. Science 1978;199:303–5.
112. Yamasalis E, Ames BN. Cancer of mutagens from urine by absorption with the nonpolar resin XAD-2: cigarette smokers have mutagenic urine. Proc Natl Acad Sci U S A 1977;74: 3555–9.
113. Petrakis NL, Maack CA, Lee RE, et al. Mutagenic activity in nipple aspirates of human breast fluid. (Letter). Cancer Res 1980;40:188–9.

114. Sasson IM, Haley NJ, Hoffmann D, et al. Cigarette smoking and neoplasia of the uterine cervix: smoke constituents in cervical mucus. (Letter). N Engl J Med 1985;312:315–16.
115. Ferson M, Edwards A, Lind A, et al. Low natural killer-cell activity and immunoglobulin levels associated with smoking in human subjects. Int J Cancer 1979;23:603–9.
116. Holly EA, Petrakis NL, Friend NF, et al. Mutagenic mucus in the cervix of smokers. J Natl Cancer Inst 1986;76:983–6.
117. Hellberg D, Nilsson S, Haley NJ, et al. Smoking and cervical intraepithelial neoplasia: nicotine and cotinine in serum and cervical mucus in smokers and nonsmokers. Am J Obstet Gynecol 1988;158:910–13.
118. Kreyberg L. Histological lung cancer types: a morphological and biological correlation. Acta Pathol Microbiol Cancer 1962;Suppl 152:1–56.
119. Schiffman MH, Haley NJ, Felton JS, et al. Biochemical epidemiology of cervical neoplasia: measuring cigarette smoke constituents in the cervix. Cancer Res 1987;47: 3886–8.
120. McArdle JP, Muller HK. Quantitative assessment of Langerhans' cells in human cervical intraepithelial neoplasia and wart virus infection. Am J Obstet Gynecol 1986;154: 509–15.
121. Tay SK, Jenkins D, Maddox P, et al. Subpopulations of Langerhans' cells in cervical neoplasia. Br J Obstet Gynecol 1987;94:10–15.
122. Stingl G, Katz SI, Clement L, et al. Immunologic functions of Ia-bearing epidermal Langerhans cells. J Immunol 1978; 121:2005–13.
123. Barton SE, Jenkins D, Cuzick J, et al. Effect of cigarette smoking on cervical epithelial immunity: a mechanism for neoplastic change? Lancet 1988;2:652–4.
124. Jones CJ, Schiffman MH, Kurman R, et al. Elevated nicotine levels in cervical lavages from passive smokers. Am J Public Health 1991;81:378–9.
125. Basu J, Mikhail MS, Palan PR, et al. Factors influencing the exfoliation of cervicovaginal epithelial cells. Am J Obstet Gynecol 1992;167:1904–9.
126. McCann MF, Irwin DE, Walton LA, et al. Nicotine and cotinine in the cervical mucus of smokers, passive smokers, and nonsmokers. Cancer Epidemiol Biomarkers Prev 1992; 1:125–9.
127. Holly EA, Cress RD, Ahn DK, et al. Characteristics of women by smoking status in the San Francisco Bay area. Cancer Epidemiol Biomarkers Prev 1992;1:491–7.
128. Holly EA, Cress RD, Ahn DK, et al. Detection of mutagens in cervical mucus in smokers and nonsmokers. Cancer Epidemiol Biomarkers Prev 1993;2:223–8.
129. Simons AM, Phillips DH, Coleman DV. Damage to DNA in cervical epithelium related to smoking tobacco. BMJ 1993; 306:1444–8.
130. King MM, Hollingsworth A, Cuzick J, et al. The detection of adducts in human cervix tissue DNA using 32P-postlabelling: a study of the relationship with smoking history and oral contraceptive use. Carcinogenesis 1994;15: 1097–100.
131. Simons AM, Phillips DH, Coleman DV. DNA adduct assay in cervical epithelium. Diagn Cytopathol 1994;10:284–8.
132. Warwick AP, Redman CWE, Jones PW, et al. Progression of cervical intraepithelial neoplasia to cervical cancer: interactions of cytochrome P450 CYP2D6 EM and glutathione s-transferase GSTM1 null genotypes and cigarette smoking. Br J Cancer 1994;70:704–8.
133. Goldacre M, Vessey M, Clarke J, et al. Record linkage study of morbidity following vasectomy. In: Lepow IH, Crozier R, eds. Vasectomy: immunologic and pathophysiologic effects in animals and man. New York, NY: Academic Press, 1979: 567–75.
134. Walker AM, Jick H, Hunter JR, et al. Hospitalization rates in vasectomized men. JAMA 1981;245:2315–17.
135. Petitti DB, Klein R, Kipp H, et al. Vasectomy and the incidence of hospitalized illness. J Urol 1983;129:760–2.
136. Massey FJ Jr, Bernstein GS, O'Fallon WM, et al. Vasectomy and health: results from a large cohort study. JAMA 1984; 252:1023–9.
137. Ross RK, Paganini-Hill A, Henderson BE. The etiology of prostate cancer: what does the epidemiology suggest? Prostate 1983;4:333–44.
138. Honda GD, Bernstein L, Ross RK, et al. Vasectomy, cigarette smoking, and age at first sexual intercourse as risk factors for prostate cancer in middle-aged men. Br J Cancer 1988;57:326–31.
139. Newell GR, Fueger JJ, Spitz MR, et al. A case-control study of prostate cancer. Am J Epidemiol 1989;130:395–8.
140. Sidney S. Vasectomy and the risk of prostatic cancer and benign prostatic hypertrophy. J Urol 1987;138:795–7.
141. Rosenberg L, Palmer JR, Zauber AG, et al. Vasectomy and the risk of prostate cancer. Am J Epidemiol 1990;132: 1051–5.
142. Mettlin C, Natarajan N, Huben R. Vasectomy and prostate cancer risk. Am J Epidemiol 1990;132:1056–61.
143. Guess HA. Invited commentary: vasectomy and prostate cancer. Am J Epidemiol 1990;132:1062–5.
144. Howards SS. American Urological Association response to two articles on the relationship of vasectomy and prostate cancer. Oncology 1991;5:78–80.
145. Vasectomy and cancer. (Noticeboard). Lancet 1991;338: 1586.
146. Hayes RB, Pottern LM, Greenberg R, et al. Vasectomy and prostate cancer in US blacks and whites. Am J Epidemiol 1993;137:263–9.
147. Rosenberg L, Palmer JR, Zauber AG, et al. The relation of vasectomy to the risk of cancer. Am J Epidemiol 1994;140: 431–8.
148. Hsing AW, Wang RT, Gu FL, et al. Vasectomy and prostate cancer risk in China. Cancer Epidemiol Biomarkers Prev 1994;3:285–8.
149. John EM, Whittemore AS, Wu AH, et al. Vasectomy and prostate cancer: results from a multiethnic case-control study. J Natl Cancer Inst 1995;87:662–9.
150. Zhu K, Stanford JL, Daling JR, et al. Vasectomy and prostate cancer: a case-control study in a health maintenance organization. Am J Epidemiol 1996;144:717–22.
151. Sidney S, Quesenberry CP, Sadler MC, et al. Vasectomy and the risk of prostate cancer in a cohort of multiphasic health-checkup examinees: second report. Cancer Causes Control 1991;2:113–16.
152. Nienhuis H, Goldacre M, Seagroatt V, et al. Incidence of disease after vasectomy: a record linkage retrospective cohort study. BMJ 1992;304:743–6.
153. Giovannucci E, Tosteson TD, Speizer FE, et al. A long-term study of mortality in men who have undergone vasectomy. N Engl J Med 1992;326:1392–8.
154. Giovannucci E, Ascherio A, Rimm EB, et al. A prospective cohort study of vasectomy and prostate cancer in US men. JAMA 1993;269:873–7.
155. Giovannucci E, Tosteson TD, Speizer FE, et al. A retrospective cohort study of vasectomy and prostate cancer in US men. JAMA 1993;269:878–82.
156. Hiatt RA, Armstrong MA, Klatsky AL, et al. Alcohol consumption, smoking and other risk factors and prostate cancer in a large health plan cohort in California (United States). Cancer Causes Control 1994;5:66–72.
157. Moller H, Knudsen LB, Lynge E. Risk of testicular cancer after vasectomy: cohort study of over 73,000 men. BMJ 1994;309:295–9.
158. DerSimonias R, Clemens J, Spirtas R, et al. Vasectomy and prostate cancer risk: methodological review of the evidence. J Clin Epidemiol 1993;46:163–72.
159. Skegg DCG. Vasectomy and risk of cancers of prostate and testis. Eur J Cancer 1993;29A:935–6.
160. Boyle P, Zardize DG. Risk factors for prostate and testicular cancer. Eur J Cancer 1993;29A:1048–55.

161. Howards SS. Possible biological mechanisms for a relationship between vasectomy and prostatic cancer. Eur J Cancer 1993;29A:1060–2.
162. Pienta KJ, Esper PS. Risk factors for prostate cancer. Ann Intern Med 1993;118:793–803.
163. AVSC technical statement: vasectomy and prostate cancer. Washington, DC: Association for Voluntary Surgical Contraception, 17 February, 1993.
164. NICHD, NCI, NIDDK final statement—Vasectomy and Prostate Cancer Conference. Bethesda, MD: National Institute of Child Health and Human Development, National Cancer Institute, National Institute of Diabetes and Digestive and Kidney Diseases, March 2, 1993.
165. Raspa RF. Complications of vasectomy. Am Fam Physician 1993;48:1264–8.
166. Klitsch M. Vasectomy and prostate cancer: more questions than answers. Fam Plann Perspect 1993;25:133–5.
167. Howards SS, Peterson HB. Vasectomy and prostate cancer: chance, bias, or a causal relationship? (Editorial). JAMA 1993;269:913–14.
168. Farley TMM, Meirik O, Mehta S, et al. The safety of vasectomy: recent concerns. Bull World Health Organ 1993; 71:413–19.
169. Healy B. Does vasectomy cause prostate cancer? JAMA 1993;269:2620.
170. Guess HA. Is vasectomy a risk factor for prostate cancer? Eur J Cancer 1993;9A:1055–60.
171. Skegg D. Vasectomy and prostate cancer: is there a link? N Z Med J 1993;106:242–3.
172. Pollack AE. Vasectomy and prostate cancer. Adv Contracept 1993;9:181–6.
173. Howards SS. Vasectomy and prostate cancer. West J Med 1994;160:166–7.
174. Wildschut HIJ, Monincx W. Vasectomy and the risk of prostate cancer. (Point of View). Bull World Health Organ 1994;72:777–8.
175. Tripathy SP, Ramachandran CR, Ramachandran P. Health consequences of vasectomy in India. Bull World Health Organ 1994;72:779–82.
176. Hayes RB. Are dietary fat and vasectomy risk factors for prostate cancer? J Natl Cancer Inst 1995;87:629–30.
177. Key T. Risk factors for prostate cancer. In: Cancer surveys. Preventing prostate cancer: screening versus chemoprevention. Vol 23. Oxford, England: Imperial Cancer Research Fund, 1995:63–77.
178. Weed DL. Methodologic guidelines for review papers. J Natl Cancer Inst 1997;89:6–7.
179. Weed DL. Meta-analysis under the microscope. J Natl Cancer Inst 1997;89:904–5.
180. Weed DL. The behavior biology interface in cancer prevention and control. Prev Med 1997;26:S37–41.
181. Susser M, Susser E. Choosing a future for epidemiology. II. From black box to Chinese boxes and eco-epidemiology. Am J Public Health 1996;86:674–7.